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Spinal and bulbar muscular atrophy (SBMA) is a motor neuron disease caused by polyglutamine expansion mutation in the androgen receptor (AR). Since skeletal muscle mitochondrial dysfunction was observed in neuromuscular disorders and may play a role in disease progression, we assessed the effect of mutant AR on the transcription of mitochondrial proteins in muscle tissue of ten SBMA patients and of age–gender matched controls. We found a similar expression of AR in SBMA muscle tissues compare the controls. On the contrary, immunohistochemistry and western blot analysis revealed a significant 4-fold increase of AR protein level in the nuclei of SBMA patients ($p<0.01$).

When compared with healthy control subjects, patients with SBMA had similar levels of mRNA and protein of PGC-1a, TFAM, MnSod as well as a similar amount of mRNA of PGC-1b, ERRa, NRF1, mitofusin 1 and mitofusin2. Taken together these results show that in human SBMA skeletal muscle, mutant AR did not affect expression and presence of mitochondrial proteins. Notably we found a 48% reduction in mtDNA copy number ($p<0.03$), compare to controls and to muscle of eight patients with amyotrophic lateral sclerosis (ALS), suggesting a specific involvement of mutant AR in the mtDNA homeostasis.

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21P16

The role of mitochondria in cell death — Regulation of the pro-apoptotic protein Bak

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Apoptosis or programmed cell death is essential for embryonic development as well as cellular homeostasis and many other mechanisms in multicellular organisms. Although many studies have elucidated several molecular mechanisms of the regulation of apoptosis and the role of Bax and Bak involved, the detailed mechanism remains not fully understood. As Bak is localized at the mitochondrial outer membrane it requires continuous regulation to prevent uncontrolled apoptosis. This is controlled, in part, due to its association with the porin VDAC2. Studies into the mode of interaction between Bak and VDAC2 and aspects to the mechanism of regulation will be presented.

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21P17

Genotype/phenotype correlations in fibroblasts of patients with pathogenic *POLG*-mutations

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Mitochondria possess their own double-stranded DNA which is replicated by an assembly of nuclear encoded proteins including polymerase gamma (*POLG*) as the sole replicase, also involved in mtDNA repair [1].

Pathogenic mutations in *POLG* are known to be associated with different neurodegenerative disorders, e.g. Alpers–Huttenlocher syndrome and CPEO [2,3]. Until now the impact of *POLG* mutations on the biochemical phenotype remains enigmatic.

MtDNA copy numbers were determined in fibroblasts of two *POLG* patients exhibiting mild to severe clinical phenotypes. The first patient (p1), carrying heterozygous mutations in the linker domain (p.Arg627Trp; p.Trp748Ser) showed a mild clinical phenotype whereas the second patient (p2), harboring a homozygous mutation in the polymerase domain (Arg1096Cys), showed a severe phenotype (multifocal therapy-refractory epilepsy, reduced mtDNA copy number and multiple deletions in muscle). Both patients exhibited a slight but not significant decrease in their mtDNA content in fibroblasts. Measurements of respiration rates (ADP-stimulated) revealed no significant differences in any of the two cell lines compared to controls.

To examine these findings in detail, fibroblasts of p2 and a control line were depleted of mtDNA by long-term treatment with 20 μM ddC, followed by a repopulation phase. In both phases oxygen consumption and mtDNA content were measured. During depletion mtDNA content and respiration rates were significantly diminished in both lines. In contrast to controls, in *POLG* fibroblasts both mtDNA copy number and respiration rates remained low during a 65 day repopulation phase.

Our results strongly indicate that the respiration rates correlate directly with the mtDNA copy number.

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21P18

The subcellular localization of inorganic pyrophosphatases is a crucial issue to properly understand their physiological roles

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The hydrolysis of inorganic pyrophosphate (PPi), an ubiquitous energy-rich metabolite, is required for most anabolic reactions to proceed. This essential reaction (EC 3.6.1.1) is catalyzed by two major classes of non-homologous proteins globally named pyrophosphatases (PPases): the widely-distributed soluble PPases (sPPases) that simply hydrolyse PPi, and the ion-pumping membrane PPases, H^+(or Na^+)-PPases, that couple PPi-hydrolysis to the generation of transmembrane electrochemical gradients. sPPases are located in fungal and animal cells cytosol, and in energy-converting organelles (mitochondria, chloroplasts), but are absent in cytosol of photosynthetic plant cells, where membrane PPases do work instead of them. These PPases conform to the simplest class of primary ion pumps known to date, allowing PPi usage as a "low-cost" energy currency alternative to ATP [1].

We optimized the heterologous expression of diverse membrane PPases in yeast by manipulating their N-terminal domains with